REMARKS

The Specification

Objections have been raised to the specification. These objections are respectfully traversed.

An objection to specification has been made because page 12, line 1 uses "tetp" and "ptet" interchangeably. An amendment has been made herein to replace "ptet" with --tetp--.

Objections have been raised against the specification because the specification and figures use "TAKON" and "TET-ON" interchangeably. "TAKON" is an alternative designation for "TET-ON". To avoid future confusion, the specification and figures 1 and 2 have been amended to replace all instances of "TAKON" to --TET-On--. Changes to the figures are indicated in red on the enclosed copies. The only changes made have been to replace "TAKON" with --TET-ON-- in Figures 1 and 2. The Applicants respectfully request that the objections to the specification be withdrawn.

Sequence Compliance

A "Notice to Comply with Requirements for Patent Application Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures" has been issued for the above referenced patent application. This requirement is respectfully traversed.

The Examiner has stated that the above referenced application contains sequence disclosures that are encompassed by the definitions for nucleotide and amino acids sequences under 35 C.F.R. §1.821(a)(1) and (a)(2). The Applicant respectfully disagrees. The specification and claims make references to specific segments of known sequences but no actual sequences are disclosed in the application. The referenced sequences are sequences from promoters, gene, plasmid constructs etc. well known to those of skill in the art. There is no requirement to list the actual sequences. These sequences are disclosed by the common names of these known genes, promoters, and constructs and are not sequence disclosures per se. For example, TAKON is not a sequence but is rather the name of a nucleotide binding protein. SCID is the name of a strain of mouse. TET-ON is the name of a well known fusion protein. bHLHLZ is a the name of a protein domain. As no actual

sequences are disclosed in the instant application, the Applicant respectfully requests that the "Notice to Comply with Requirements for Patent Application Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures" be withdrawn.

The 35 U.S.C. §112 Rejections

Claims 1-3 stand rejected under 35 USC §112, second paragraph as incomplete. This rejection is respectfully traversed.

The Examiner argues that claims 1-3 omit essential elements, which amounts to a gap between the elements. First of all, the Examiner cites claim 1 for failing to describe where the heterologous gene is to inserted into the vector. Claim 1 has been amended to more clearly state the nature of the various components of the pDATH-X vector. All of these elements enabled are described in detail in the legend to Figure 1 on pages 11-12 of the specification. This amendment includes a detailed description of the cloning site for the heterologous genes.

The Examiner also argues that the vector of claims 2 and 3 needs to be further delineated. Claim 2 has been amended to state

that the vector is the pDATH-X vector of claim 1. As claim 3 is dependent upon claim 2, this limitation is incorporated therein as well.

The described amendments to claims 1 and 2 incorporate all missing steps into claims 1-3. The Applicants respectfully request that the 35 USC §112, second paragraph rejection of claims 1-3 be withdrawn.

Claims 2 and 3 stand rejected under 35 USC §112, first paragraph, as unenabled for sustained expression of genes *in vivo*. This rejection is respectfully traversed.

First of all, the pending claims are not directed to obtaining sustained expression but rather to allow the localized, temporal expression in an area of the body to be treated. Therefore, claim 2 has been amended to replace "sustained expression" with --localized, temporal expression--.

The Examiner cites **Crystal** (*Science*, 270:404-410, 1995), **Friedman** (*Scientific American*, June 1997, pp 96-101), **Branch** (TIBS, 23:45-50, 1998), **Crooke** ("Principles of Antisense Therapeutics," In: Antisense Research and Application, Springer-Verlag, 1998, pp. 1-50), **Schofield** *et al.* (*British Medical*

Bulletin, 51:56-71, 1995), and **Verma** *et al.* (*Nature*, 389: 239-242, 1997) as evidence of the unpredictability of *in vivo* gene delivery and gene therapy. Obstacles include problems in adequate delivery of the molecules to sufficient numbers of cells, cell targeting, and gene expression within target cells. Specificity of targeting is not an issue as the vector of the instant invention can be administered generally but will remain inactive until activated by heat or light. As a result, specificity of expression can be achieved without the need for tissue specific expression elements. Although it is true the pharmacokinetics of tetracycline vary within individual organisms as well within tissues of a given individual, cells that receive the vector should be able to express the heterologous gene over a broad range of tetracycline concentrations without undue experimentation.

The vector of the instant invention provides a powerful expression system that overcomes many of problems of poor expression within the target tissue. Furthermore, the instant invention does not claim to solve all problems associated with gene delivery and gene therapy but offers a powerful expression system for the uses therein. The instant invention will provide a useful system for the regulable expression of therapeutic

transgenes. Accordingly, the Applicants respectfully request that the 35 USC §112, first paragraph, rejection of claims 2 and 3 as unenabled be withdrawn.

The 35 USC §103 Rejection

Claims 1-3 stand rejected under 35 USC §103(a) as obvious over the combination of **Reeves** *et al.* (U.S. Patent No. 5,965,440, Oct. 12, 1999) and **Cigan** *et al.* (U.S. Patent No. 6,072,102, June 6, 2000) in view of **Voellmy** *et al.* (Proc. Natl. Acad. Sci. U.S.A., 82:4949-4953, 1985), and further in view of **Szafranski** *et al.* (U.S. Patent No. 6,124,129, Sept. 26, 2000). This rejection is respectfully traversed.

Reeves *et al.* teaches a tetracycline regulable retroviral vector for the expression of heterologous gene in mammalian cells. **Cigan** *et al.* teaches a dominant negative regulator linked to a binding site for a transcription activating fusion protein. **Voellmy** *et al.* cloning of a heat shock protein gene segment including the heat shock activated genetic elements regulating expression of the gene. **Szafranski** teaches methods of fully inhibiting leaky promoters with antisense constructs. While **Reeves** *et al.*, **Cigan** *et*

al., **Voellmy** *et al.* and **Szafranski** *et al.* teach the individual components of the instant invention, these references do not enable the construction of a vector encompassing all of these elements without undue additional experimentation. The fact that four separate references have to be combined to encompass all of the separate elements of the instant invention is in itself strong evidence against obviousness of the instant invention.

Dramatic effects on gene expression can result from small changes in regulatory sequences. One of skill in the art would have no way of knowing beforehand whether the combination would be effective without actually constructing the combination and testing its effects on the expression of a reporter or heterologous gene. This would constitute undue experimentation beyond what would be obvious to one of ordinary skill in the art. In particular, none of the references teach the fusion of a heat shock and tetracycline regulable promoters. It is possible that the combined promoters would fail to work together to stimulate gene expression. In addition, without additional experimentation, one of skill in the art would not know whether expression from the construct was leaky or ineffective. Therefore, the Applicants respectfully request

that the 35 USC §103(a) rejection of claims 1-3 as obvious over the combination of **Reeves** *et al.* and **Cigan** *et al.* in view of **Voellmy** *et al.* and further in view of **Szafranski** *et al.* be withdrawn.

This is intended to be a complete response to the Office Action mailed October 24, 2000. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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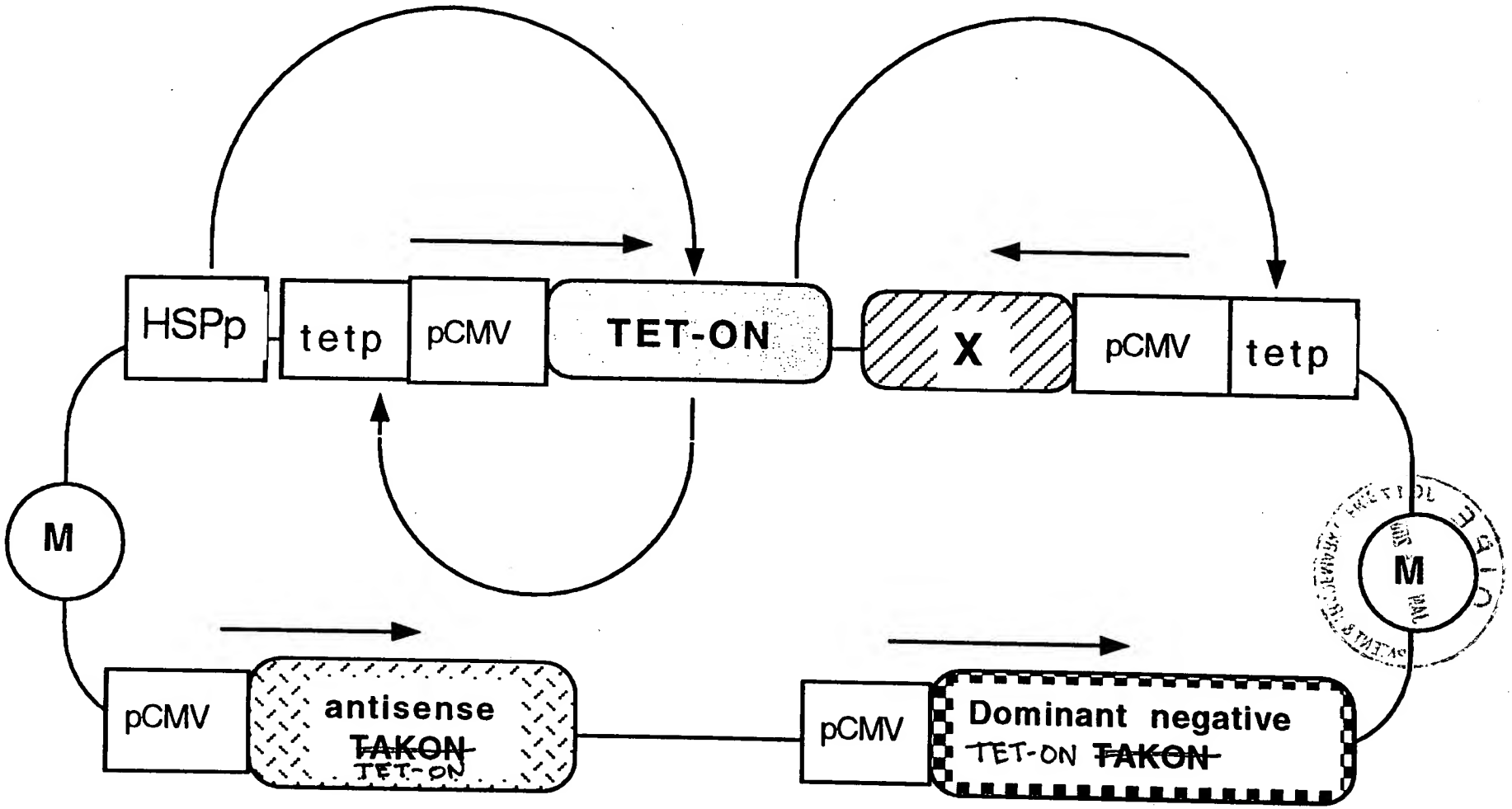
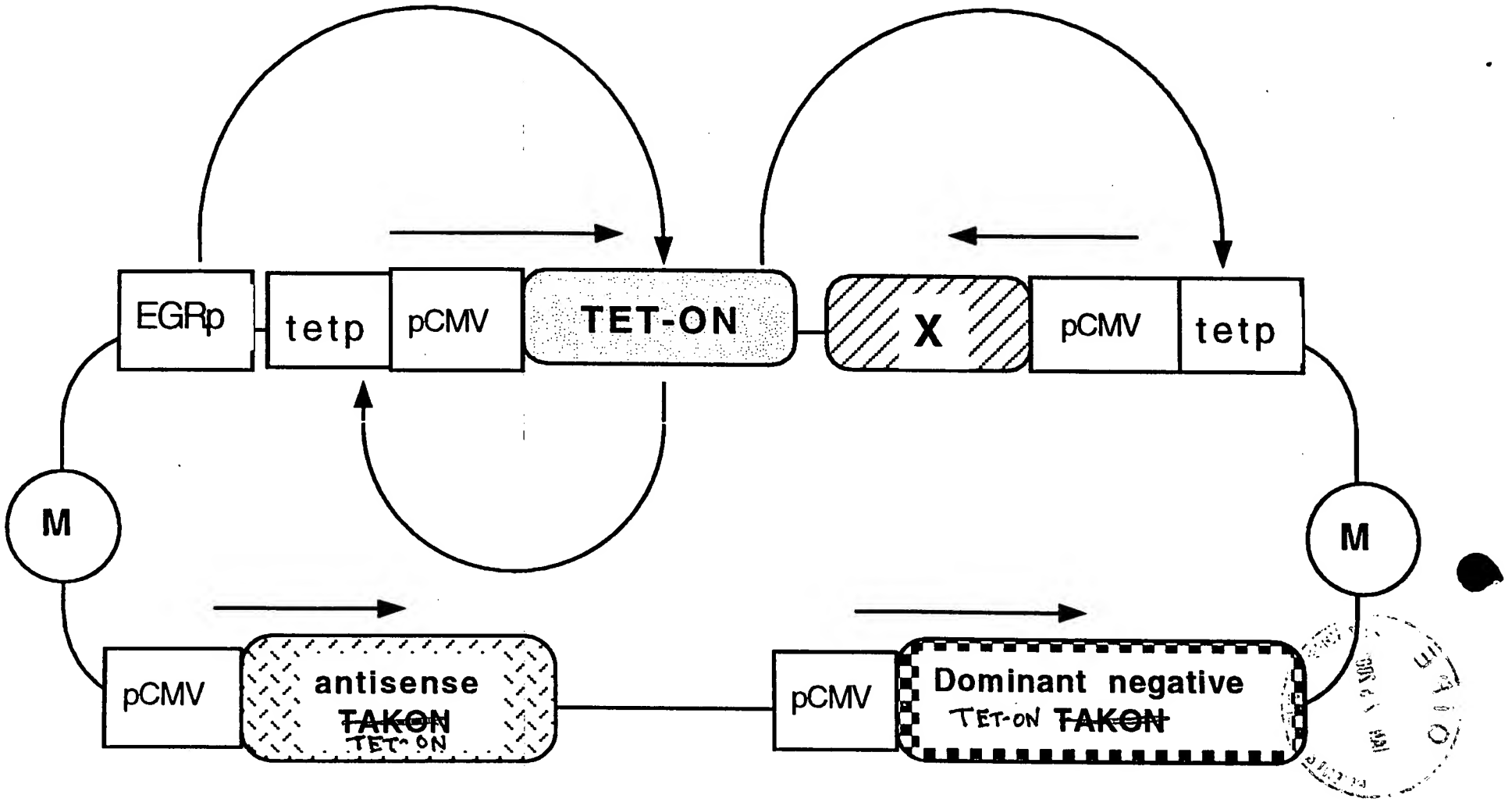

HSPp
tetp
pCMV
TET-ON
X
pCMV
tetp
M
M
pCMV
antisense
TAKON
TET-ON
pCMV
Dominant negative
TET-ON TAKON

FIG. 1


EGRp
tetp
pCMV
TET-ON
X
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tetp
M
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antisense
TAKON
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Dominant negative
TET-ON TAKON

FIG. 2